PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC11728A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2005/000010	International filing date *(day/month/year)* 06.01.2005	Priority date *(day/month/year)* 30.01.2004
International Patent Classification (IPC) or national classification and IPC INV. A61K31/439 A61P39/00 A61P41/00		
Applicant PFIZER PRODUCTS INC. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.02.2005	28.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Loher, F Telephone No. +49 89 2399-7839

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2005/000010

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-16	as originally filed

Claims, Numbers

11-20	as originally filed
1-10	received on 30.11.2005 with letter of 28.11.2005

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 and 3-9 (IA)

because:

☒ the said international application, or the said claims Nos. 1 and 3-9 (IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 4, 5, 8
	No:	Claims	1, 2, 6, 7, 9, 10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	2, 10
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1 and 3-9 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO03/009848
D2: WO03/0073304
D3: GARDNER C ET AL: Inhibition of anaesthetic-induced emesis by a NK1 or 5-HT3 receptor antagonist in the house musk shrew, Suncus murinus. NEUROPHARMACOLOGY 1998 UNITED KINGDOM (37):1643-1644.
D4: DIEMUNSCH P ET AL: Antiemetic activity of the NK1 receptor antagonist GR205171 in the treatment of established postoperative nausea and vomiting after major gynaecological surgery. BRITISH JOURNAL OF ANAESTHESIA 1999 UNITED KINGDOM (82):274-276.

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

Art 33(2) The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 1, 2, 6, 7, 9 and 10 is not new.
In interpreting claims 1-9 for determining novelty, the diseases to be treated are decisive. The discovery of a new mechanism of action even if representing an important piece of scientific knowledge, still needs to find a practical application in the form of a defined, real treatment of a pathological condition in order to make a technical contribution to the art and be considered as an invention eligible for patent protection. A new mechanism of action is only relevant with respect to novelty of a claim directed to a second medical use of a known compound or composition, in so far as this mode of action results in a new use of the known product. This new use is the technical feature which must be included in the wording of the respective claims.
In interpreting claim 10 for determining novelty, non distinctive characteristics of a particular intended use should be disregarded. Hence, the subject matter of claim 10 discloses nothing more than the composition *per se*.

D1 discloses a pharmaceutical composition for parenteral administration comprising maropitant citrate (present compound 1a) for the treatment of anxiety. Therefore, the subject-matter of claim 10 is not new in the light of D1.

D2 discloses a pharmaceutical composition for parenteral administration comprising maropitant citrate (present compound 1a) for the treatment of emesis. Therefore, the subject-matter of claim 10 is not new in the light of D2.

Both D3 and present claim 1 disclose the administration of a NK-1 receptor antagonist to improve anaesthesia recovery. So the patient groups to be treated at least do overlap or even are in no way different. Therefore, the subject-matter of claims 1, 2, 6, 7, 9 and 10 is not new in the light of D3.

Both D4 and present claim 1 disclose the administration of a NK-1 receptor antagonist to improve anaesthesia recovery. So the patient groups to be treated at least do overlap or even are in no way different. Therefore, the subject-matter of claims 1, 2, 6, 7, 9 and 10 is not new in the light of D4.

Art 33(3) The present application does not meet the requirements of Article 33(3) PCT, since the subject-matter of claims 1-10 does not seem to involve an inventive step.

D3 and D4 disclose that NK-1 receptor antagonists are useful agents for improving anaesthesia recovery.

The problem to be solved by the present invention may therefore be regarded as how to provide another medicament for improving anaesthesia recovery.

The present application suggests to solve the problem posed by providing a NK-1 receptor antagonist (maropitant citrate).

D1 and D2 teaches that maropitant is a NK-1 receptor antagonist and that NK-1 receptor antagonists are useful antiemetic agents, emesis being one symptom which occurs during anaesthesia recovery.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of claims 1, 2, 6, 7, 9 and 10 the applicant's attention is drawn to the fact that even if novelty could be established over the above-cited prior art it is at present not clear wherein an inventive step may reside.

With respect to the subject-matter of claims 3, 4, 5 and 8 the applicant's attention is drawn to the fact that there seems to be no basis for inventive step within the present application as filed since no evidence can be found that the features which are novel result in a solution of the posed problem which could not have been foreseen by the skilled person.

Being aware of the teaching of D3 and D4 the skilled person perfomed an arbitrary choice out of one list containing all NK-1 receptor antagonists to select those of the present application in order to use them to improve anaesthetic recovery. The finding that those compounds do also reduce purposeless movements and excessive vocalisation is considered to be a bonus effet which would have been inevitably discovered by everybody who followed the teaching of D1-D4 and administered NK-1 receptor antagonists in order to improve anaesthetic recovery.

It is therefore noted, that the solution proposed in claims 1-10 of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art 33(4) For the assessment of the present claims 1 and 3-9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

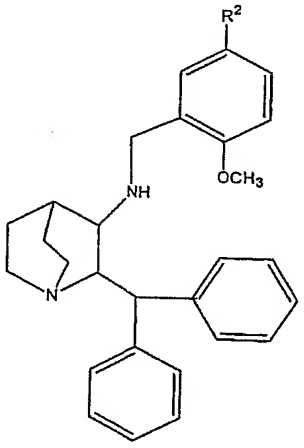
The subject-matter of claims 2 and 10 is considered to be industrially applicable in the sense of Art 33(4) PCT.

CLAIMS

1. A method of improving the quality of anesthetic recovery by reducing excessive vocalization and/or purposeless movement comprising the step of administering to an animal in need of such treatment a therapeutically effective amount of a pharmaceutical composition of a NK-1 receptor antagonist; a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.

2. The use of a NK-1 receptor antagonist; a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug, in the manufacture of a medicament for improving the quality of anesthetic recovery by reducing excessive vocalization and/or purposeless movement.

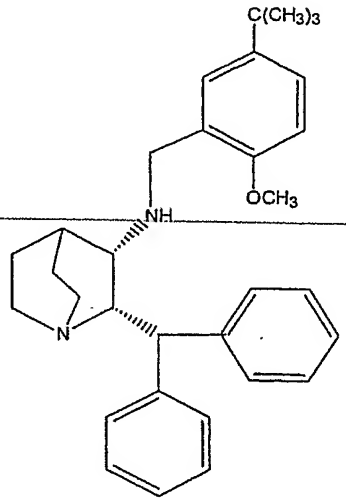
3. A method or use according to Claim 1 or Claim 2 wherein the NK-1 receptor antagonist is a compound of Formula I



I

wherein R^2 is selected from the group consisting of methyl, ethyl, isopropyl, *sec*-butyl and *tert*-butyl, or a pharmaceutically acceptable salt thereof.

4. A method or use according to Claim 3 wherein the compound of Formula I is a compound of Formula Ia,



Ia

(2*S*,3*S*)-2-benzhydryl-*N*-(5-*tert*-butyl-2-methoxybenzyl)quinuclidin-3-amine, or a pharmaceutically acceptable salt thereof.

5. The method or use according to Claim 4 wherein the compound is the citrate salt of the compound of Formula Ia.

6. The method or use according to any previous claim wherein the composition is parenterally, enterally or orally administered prior, during or after an administration of a general anesthesia.

7. The method or use according to Claim 6 wherein the composition is administered parenterally.

8. The method or use according to Claim 7 wherein the composition further comprises a pharmaceutically acceptable cyclodextrin.

9. The method or use according to Claim 7 or Claim 8 wherein the amount of the NK-1 antagonist is 0.01 mg/kg to 100 mg/kg of a patient's body weight.

10. A pharmaceutical composition for improving the quality of anesthetic recovery by reducing excessive vocalization and/or purposeless movement comprising a NK-1 receptor antagonist; a pharmaceutically acceptable salt thereof, a prodrug of said compound or said salt, or a solvate or hydrate of said compound, said salt or said prodrug.